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Original Research Article

A prospective randomized comparative study of the efficacy of sustained release vaginal insert versus intracervical gel in primigravidae at term pregnancy

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ABSTRACT

Background: Induction of labour is the intentional initiation of labour before spontaneous onset for the purpose of delivery of fetoplacental unit. Failure of induction is responsible for increased incidence of caesarean delivery. This study performed to assess and compare the clinical effects of sustained release vaginal insert versus intracervical gel in primiparous women with term pregnancy in terms of improvement of Bishop's score, Induction delivery interval, incidence of hyperstimulation, maternal and neonatal outcomes.
Methods: A total 100 consecutive term pregnant women who underwent labor induction for fetal or maternal indications were divided randomly into two groups. Group A - sustained release Vaginal insert and Group B - Intracervical gel. Informed consent was taken from each patient.
Results: Statistically significant increase in final Bishop's score (p=0.008) and hyperstimulation (p=0.04) was seen in Vaginal insert group as compared to Intracervical gel group, while there were no statistically significant differences in maternal outcomes, neonatal outcomes and need for oxytocin augmentation in both groups.
Conclusions: In this study we found that insert did not improve the induction delivery interval or rate of successful induction, nor did it have any advantage in terms of neonatal outcome although it did improve the Bishops score – Its advantage was in terms of single application, few prevaginal examinations, longer duration of action and immediate retrieval in case of hyperstimulation. Its main drawback remained the maintenance of cold chain without which its efficacy decreases. Another significant observation was the dropout rate of insert (16%).

Keywords: Bishops score, Dinoprostone, Hyperstimulation, Induction of labor

INTRODUCTION

Induction of labor, a common practice in pregnant woman throughout the world and in India, accounts for 20% of all births. It is generally indicated when the risk to either the mother or the fetus outweighs the possible benefits of continuing to manage the pregnancy.

Cervical ripening should be promoted prior to induction of labor in order to increase the likelihood of successful induction in cases with unfavourable cervix. Prostaglandins are efficient in cervical ripening and labor induction. Various recommended pharmacological methods of induction approved by different organizations are given below (Table 1).

Low Bishop's score leads to higher incidence of prolonged labour and caesarean section.[1] Dinoprostone (PGE2) has been shown to be the most effective agent in achieving cervical ripening.[2,3] Externally applied

prostaglandins are effective for cervical ripening and they hasten the delivery but also elevate the risk of uterine hyper stimulation and produce fetal heart rate changes.[4]

FDA approved vaginal insert in 1995 for cervical ripening. Its novel design provides a controlled- release formulation which supplies a continuous low dose of Dinoprostone for cervical ripening. It releases Dinoprostone at the rate of 0.3 mg/hours for 24 hours.[5,6] Sustained releasing nature of vaginal insert formulation due to addition of polyethylene oxide - absorbs water and releases Dinoprostone at a controlled rate. Furthermore, because of the integral retrieval system, Dinoprostone vaginal insert can be easily and quickly removed at the end of the 24-hour dosing period or once the onset of active labour has begun or in case of hyperstimulation. This sustained release formulation of Dinoprostone is believed to diminish the risk of uterine hyper stimulation and can be extracted rapidly. In addition, progressive cervical ripening induced by the sustained release Dinoprostone may be more tolerable to the patients than the quick onset of contractions observed with the other Dinoprostone forms.[7]

Table 1: Various recommendations for induction.

Recommendations for induction	
RCOG recommendations	Vaginal PGE2 (tablets, gel or controlled release pessary)
	Misoprostol (only for IUD or in the context of a clinical trial)
	Mifepristone (only for IUD)
	Membrane sweeping
ACOG recommendations	Prostaglandin E analogues
	Low dose (0.5-2 mu/min) oxytocin regimen
	High dose (6 mu/min) oxytocin regimen
	Vaginal Misoprostol before 28 weeks of gestation
WHO recommendations	Oral Misoprostol (25 µg, 2-hourly)
	Low-dose vaginal misoprostol (25 µg, 6-hourly)
	Intracervcal or vaginal Dinoprostone
	Balloon catheter
	Intravenous oxytocin
	Membranes sweeping

Sustained release Dinoprostone vaginal insert remains for up to 24 hours, allowing longer induction and also promotes uterine tonicity.[8] The pessary should remain sealed in the foil package and stored in a freezer (-10 to -200C) until needed. After opening it is then held between the index and middle fingers and is positioned transversely, high in the posterior fornix. The above features make the insertion an attractive option and hence worth comparing with previous established option of gel.

Cerviprime gel is Dinoprostone 0.5 mg available in a 2.5 ml disposable syringe with a catheter for endocervical application. It should be stored in refrigerator between 2-80 C. With the women in supine position, tip of the prefilled syringe is placed intra-cervically and the gel is deposited just below the internal cervical os. Doses may be repeated every 6 hours with a maximum of 3 doses recommended in 24 hours. Being a gel inserted, intracervical retrieval is not possible.

This study was performed to identify the response to two formulations of Dinoprostone in Indian pregnant nulliparous women, who may have different response due to different ethnicity and different climatic conditions.

METHODS

This prospective randomized comparative study carried on 100 consecutive pregnant women who underwent labour induction for fetal or maternal indications. The duration of this study were 18 months (From March, 2017 to September, 2018).

Inclusion criteria

- Primipara
- Singleton pregnancy
- Cephalic presentation
- Bishops less than or equal to 6 with intact membranes
- Maternal age <35
- Gestational age 37 weeks to 42 weeks
- Reactive fetal non-stress test
- Medical or Obstetric indication for induction.

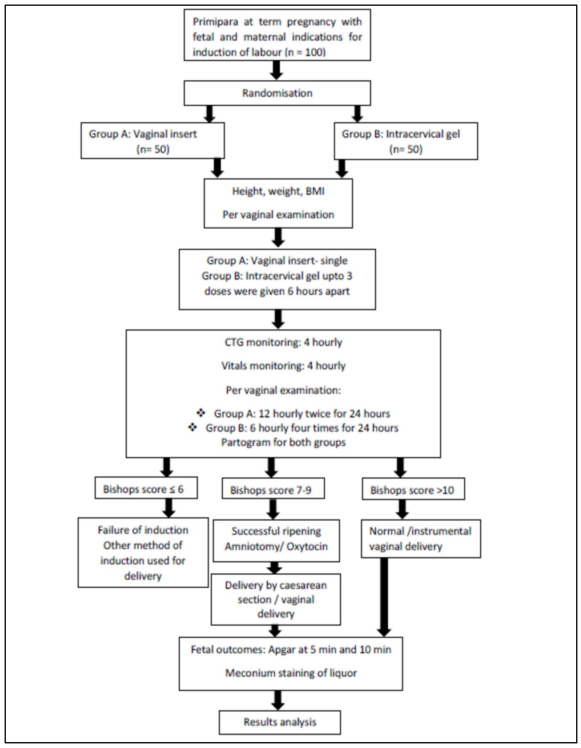
Exclusion criteria

- Pregnant women with history of previous uterine surgery
- History of bronchial asthma
- Fetal mal-presentation
- Suspected CPD
- Placenta previa
- Active vaginal bleeding
- Rupture of membranes
- Any other condition contraindicating vaginal delivery
- Women not willing to be part of trial
- Expulsion of vaginal insert before 24 hours (such women were subsequently excluded from the study).

Complete schematic Figure of study

Group A: Vaginal insert was inserted horizontally in the posterior fornix with its long axis transverse to the long axis of the vagina with aseptic precautions and time of insertion was noted. Vaginal insert was removed after 24 hours or if active labour started. Monitoring noted as shown in schematic Figure 1. Two per vaginal

examinations were done first at the end of 12 hours and next at the end of 24 hours or when active contractions started.



The insert was removed after 24 hours or earlier in the presence of;

1. Active labour (regular contractions with cervical dilatation >4 cm).
2. Spontaneous rupture of membranes.
3. Non-reassuring FHR patterns (Bradycardia, repetitive decelerations).
4. Uterine hyperstimulation defined as tachysystole ≥5 uterine contractions per 10 minutes).

Group B: Fifty people in Group B received intracervical gel. Administration and monitoring were done as shown in diagram 2.1 and 2.2. Four per vaginal examinations were done 6 hourly for 24 hours.

CTG trace was taken up-to 30 minutes immediately after insertion in both the groups followed by intermittent monitoring with CTG 4 hourly. Uterine contractions, Fetal heart rate baseline variability, accelerations and decelerations if any were noted. Uterine hyperstimulation was defined as uterine contractions lasting >2 minutes or a contraction frequency of five or more in 10 minutes. Evidence of fetal intolerance to this contraction pattern was demonstrated by late decelerations, severe variable decelerations, or fetal bradycardia, absent variability. In women with Bishop's score between 7-9 (>3 cm dilated and 60-70% effaced, with well applied fetal head) induction was continued by amniotomy or oxytocin infusion. Women with bishops score ≥10 delivered normally.

Induction delivery interval was noted. Maternal outcomes in terms of normal vaginal delivery, instrumental vaginal delivery or caesarean sections noted. Indication of caesarean, CTG abnormalities, uterine hyperstimulation, induction delivery intervals were recorded. Neonatal outcomes in terms of meconium stained liquor, Apgar score at 5 min and 10 min interval and NICU admission for more than 24 hours were recorded.

Induction failure was stated to be when Bishops score was ≤6 at the end of 24 hours from the beginning of induction and then different method of induction was started for cervical ripening. Successful ripening was defined as bishops score between 7-9 (>3 cm dilated and 60-70% effaced) at the end of 24 hours in both groups.

Statistical analysis

Data were analyzed and statistically evaluated using SPSS-PC-17 version. Quantitative data was expressed in mean, standard deviation and difference between two comparable groups were tested by student 't' test or Mann Whitney 'U' test while qualitative data were expressed in percentage. Difference between the proportions were tested by chi square test. 'P' value less than 0.05 was considered statistically significant.

RESULTS

Initial Bishop's score

Maximum women in both groups are having bishops score in the range of 0 to 4. There was no significant difference between two groups (p value = 0.25 using student t-test) (Table 2).

Final Bishop's score

Statistically significant difference was found between two groups in final Bishops score of 7-9 range group (p value = 0.008 using student t-test) (Table 3).

Table 2: Initial Bishop's score.

Initial Bishop's score	Sustained release vaginal insert (n = 50)		Intracervical gel (n = 50)		p value
	Number	Percentage	Number	Percentage	
0-4	46	92.0	47	94.0	0.25
5-6	4	8.0	3	6.0	0.69

Table 3: Final Bishop's score.

Final Bishop's score	Sustained release vaginal insert (n = 50)		Intracervical gel (n = 50)		p value
	Number	Percentage	Number	Percentage	
0-6	19	38	20	40	0.83
7-9	18	36	8	16	0.008
≥10	13	26	22	44	0.06

Maternal outcomes

Successful maternal outcomes were considered only in women who achieved cervical ripening with Dinoprostone (either vaginal insert or intracervical gel). A total of 31 women in vaginal insert group achieved successful cervical ripening (Bishops score was >7) out of which 18 delivered normally or had assisted instrumental vaginal delivery. The remaining 13 in vaginal insert group delivered by caesarean section. Whereas in intracervical gel group 30 pregnant women achieved successful cervical ripening out of which 21 women delivered normally or assisted vaginal delivery and 9 were delivered by caesarean section. However maternal outcomes were compared between two groups, there was no statistically significant difference observed when statistical analysis was done (p value > 0.05 using student t-test) (Table 4).

Table 4: Maternal outcomes.

Maternal outcomes	Sustained release vaginal insert (n = 31/50)		Intracervical gel (n = 30/50)		p value
	Number	Percentage	Number	Percentage	
NVD	14	28.0	18	36.0	0.50
Vacuum delivery	3	6.0	3	6.0	1.0
LSCS	13	26	9	18	0.45
Forceps delivery	1	2.0	0	0.0	0.44

Table 5: Incidence of hyperstimulation.

Final Bishops score at the time of hyperstimulation	Hyperstimulation in sustained release vaginal insert (n = 50)		Hyperstimulation in intracervical gel (n = 50)		p value
	N = 8	16%	N = 2	4%	
Bishops score ≤ 6	3	6.0	0	0.0	0.01
Bishops score ≥10	5	10.0	2	4.0	0.24
Total	8	16.0	2	4.0	0.04

Table 6: Incidence of meconium stained liquor.

Liquor	Sustained release vaginal insert (n = 50)		Intracervical gel (n = 50)		p value
	Number	Percentage	Number	Percentage	
Meconium stained liquor	6	12.0	2	4.0	0.138

Table 7: Need for oxytocin augmentation in study subjects.

Need for oxytocin augmentation	Sustained release vaginal insert (n = 50)		Intracervical gel (n = 50)		p value
	Number	Percentage	Number	Percentage	
Yes	20	40	15	30	0.29

Incidence of hyperstimulation

Hyperstimulation was observed in 8 out of 50 pregnant women in vaginal insert group. Bishops score was assessed at the time of removal of vaginal insert. It was ≤6 in 3 out of 8 women and ≥10 in 5 out of 8 women. Whereas hyperstimulation was seen in only 2 out of 50 women in intracervical gel group. Both these patients had Bishops score ≥10. More women in the insert group had hyperstimulation and this finding was statistically significant (p value 0.04 using student t-test) (Table 5).

Incidence of meconium stained liquor

Meconium stained liquor was noted in 6 women out of 50 women in vaginal insert group and 2 out of 50 women in intracervical gel group. However, this difference was not statistically significant. (p value - 0.138 using student t-test) (Table 6).

Need for oxytocin augmentation in study subjects

Twenty out of 50 women in vaginal insert group needed oxytocin augmentation and 15 out of 50 women needed oxytocin augmentation in intracervical gel group. No statistically significant difference was seen in both groups when the need for oxytocin augmentation was compared (p value - 0.29 using student t-test) (Table 7).

Comparison of induction delivery interval in both groups

Induction delivery interval was calculated in women who delivered normally. In both the groups none of the women delivered within 12 hours of induction. In vaginal insert group, 18 pregnant women delivered normally and induction delivery interval was between 12-24 hours in 6 and more than 24 hours in remaining 12 women. In intracervical gel group, 21 pregnant women delivered normally and induction delivery interval was between 12-24 hours in 4 and more than 24 hours in remaining 17 pregnant women. Even though induction delivery interval was shorter in vaginal insert group, no statistically significant difference was seen. (p value - 0.50 and 0.27 respectively using student t-test) (Table 8).

Table 8: Comparison of induction delivery interval in both groups.

Parameters	Sustained release vaginal insert (n = 18)		Intracervical gel (n = 21)		p value
	Number	Percentage	Number	Percentage	
Women delivered within 12 hours	0	0.0	0	0.0	1.0
12-24 hours	6	12.0	4	8.0	0.50
≥ 24 hours	12	24.0	17	34.0	0.27

Table 9: Indication for LSCS in study subjects.

Indication for LSCS	Sustained release vaginal insert (n = 13)		Intracervical gel (n = 9)		p value
	Number	Percentage	Number	Percentage	
Fetal distress	9	18	7	14	0.86
Meconium stained liquor with unfavourable Bishop's	4	8	2	4	0.71

Table 10: Comparison of neonatal outcomes.

Neonatal outcome		Sustained release vaginal insert (n = 31/50)	Intracervical gel (n = 30/50)	p value
Apgar score at 1 minutes and 5 min < 7	Number (%)	4 (8.0)	3 (6.0)	0.76
NICU Admission for > 24 hours	Number (%)	7 (14.0)	6 (12.0)	0.81

Indication for LSCS in study subjects

Nine out of 13 delivered by caesarean section in vaginal insert group due to fetal distress and the rest 4 women underwent caesarean section due to meconium stained liquor with unfavourable Bishop's score. Nine women in intracervical gel group delivered by caesarean section out of which 5 women underwent caesarean section due to fetal distress and 4 women underwent caesarean section due to meconium stained liquor with unfavourable Bishop's score. No statistically significant difference was found between two groups when indications for caesarean sections were compared (p value - 0.86 and 0.71 respectively using student t-test) (Table 9).

Comparison of neonatal outcomes

Neonatal outcomes were compared only in neonates of women who delivered vaginally with either vaginal insert or intracervical gel. Apgar score <7 was noted in 4 out of 31 neonates in vaginal insert group and 3 out of 30 neonates in intracervical gel group. 7 out of 31 neonates in vaginal insert group needed NICU admission for >24 hours and 6 out of 30 neonates in intracervical gel group needed NICU admission >24 hours. When neonatal outcomes were compared no statistically significant difference was found between both groups (p value - 0.76 and 0.81 respectively using student t-test) (Table 10).

DISCUSSION

The success of induction depends upon the condition of cervix. Unfavorable cervix leads to failure of induction and increases the chances of delivering by caesarean section. In the present study the effectiveness of intracervical gel and vaginal insert in primiparous women was compared by taking initial bishops score of ≤6 as inclusion criteria. Various other studies have taken Bishops score as ≤6 Mukhopadhyay et al, ≤8 Ottinger et al, ≤4 Fabio fachinetti et al.[9-11] All mentioned studies included primiparous women to compare vaginal insert and intracervical gel which was similar to this study.

Final Bishops score in this study has been divided into three groups i.e., ≤6, 7 to 9 and ≥10. Failure of induction was defined as final bishops score of ≤6. In this study failure of induction (final Bishops ≤6) was observed in 38% in vaginal insert group and in 40% in intracervical group. Whereas, final Bishops score in the range of 7-9 was more in vaginal insert group ($p<0.02$) when compared to the intracervical gel group and it was statistically significant. Present study found that vaginal insert was effective in improving bishops score in the range of 7-9 as compared to intracervical gel however percentage of women who delivered normally was higher in intracervical gel group. Hence improvement in Bishops score did not automatically translate to a more favorable outcome. Twenty-six percent (26%) of pregnant women in vaginal insert group and 44% of pregnant woman in intracervical gel group had successful vaginal delivery however this was not statistically significant.

Westgate J et al, and Trofatter KF et al, had outcomes similar to this study whereas Fachinetti F et al, Annamaria et al, compared the cervical ripening efficacy of both Dinoprostone preparations and concluded that intracervical gel was more effective than vaginal pessary in achieving cervical ripening.[11-14] Most of the above-mentioned studies included both primi and multigravidae and used vaginal insert only for 12 hours. Whereas the current study used vaginal insert for 24 hours and included only primiparous women.

Hyper-stimulation was observed in 8 (16%) pregnant women in vaginal insert group. This finding was statistically significant, while it was observed in only 1 (2%) pregnant women in intracervical gel group. However, most of the hyperstimulation was not associated with abnormal CTG patterns and when vaginal insert was removed hyperstimulation resolved spontaneously. Various studies showing incidence of hyperstimulation with vaginal insert (Table 11).

It is assumed that hyperstimulation would be minimal with vaginal insert due to sustained release of the formulation, on the contrary it was found to be higher with vaginal insert. In the current study, oxytocin augmentation was required more in vaginal insert group than intracervical gel group (34% versus 24%) but it was not statistically significant (p 0.27). However, this was contrary to the findings of Facchinetti F et al (41.4% versus 24.3%).[11] Whereas, Mukhopadhyay et al showed no significant difference in need for augmentation with in both groups.[9]

Table 11: Incidence of hyper stimulation.

Study	Incidence of hyper stimulation with vaginal insert
Present study	16%
Leo Pevzner et al[16]	27.1%
Smith et al[26]	12.1%
Miller et al[21]	10%
Witter et al[19]	7%

In the present study, incidence of caesarean delivery was more in vaginal insert group than intracervical gel group (26% versus 18%). Mazouni et al, using vaginal pessary, found that pregnant women had a 3.5 fold higher risk of caesarean section.[15] Pevzner L et al, evaluated cardiotocographic abnormalities associated with Dinoprostone vaginal insert and noticed 35% delivered by caesarean section due to CTG abnormalities with vaginal insert.[16] Similarly, higher incidence of caesarean delivery in vaginal insert as compared to intracervical gel were noted by Ottinger et al, (28.9% versus 24.4%), Stewart et al, (23.3% versus 22.1%) and Triglia et al, (31% versus 28%).[10,17,18]

Table 12: Various studies showing shorter induction delivery interval.

Studies showing shorter induction delivery interval in vaginal insert group	Studies showing Shorter induction delivery interval in Intracervical gel group
Present study	Hennessey et al,[20]
Ottinger et al,[10]	-
Witter et al,[19]	-
Miller et al,[21]	-
Stewart et al,[17]	-

Various indications for caesarean delivery in both groups (vaginal insert versus cervical gel group) as noted in the present study are fetal distress (18% versus 14%) and meconium stained liquor with unfavorable bishops (8% versus 4%). Facchinetti F et al, studied indications for cesarean were fetal distress (4% versus 8%), dystocia (6% versus 7%) and failed induction (7.1% versus 12.9%).[11] Stewart et al, noted slightly different indications like failure to progress (10% versus 10%), failed induction (1% versus 5%) and non- reassuring fetal heart rates (3% versus 4%).[17]

In the present study vaginal insert group, 12% delivered with-in 24 hours of induction as against 4% in intracervical gel group. Induction delivery interval was shorter in vaginal insert group however more number of

pregnant women in intracervical gel group delivered normally. Similarly, Ottinger et al, also observed shorter mean induction delivery interval with vaginal insert.[10] Witter et al, conducted a randomized trial of Dinoprostone vaginal pessary and observed average induction delivery interval of 27 hours.[19] In Hennessey et al, study intracervical gel was found more effective in shortening the induction-to-vaginal delivery interval than use of a controlled-release vaginal insert.[20] In the present study none of the pregnant women in both groups delivered within 12 hours. Miller et al, observed 30% of pregnant women delivered within 12 hours after induction.[21] Whereas, study by Stewart et al, 19.5% of pregnant women delivered within 12 hours.[17] These studies (Table 12) included both nulliparous and multi-gravidae and in the present study we have included only primigravida women with poor bishops score.

In the present study no pregnant women delivered neonate with Apgar <7 at 5 min in both groups and this was consistent with the findings of Vollebregt et al, Strobelt et al and El-shawarby et al.[22-24]

In vaginal insert group 14% neonates required NICU admission for more than 24 hours in this study whereas in gel group 12% required NICU admission for >24 hours. In a study by Rugarn O et al, only 3.7% of neonates had NICU admissions with vaginal insert.[25] In this study little higher incidence of meconium stained liquor seen in vaginal insert group (12% versus 4%). Rugarn O et al, found meconium stained liquor in 18.5%.[25] Stroblet et al, found more incidence of meconium stained liquor in vaginal insert group (9.1% versus 7.5%).[23]

CONCLUSION

Sustained release vaginal insert had an advantage of metered release of Dinoprostone and there was statistically significant improvement in bishops score in range of 7-9 but it did not translate into successful induction. Advantage with vaginal insert was immediate retrieval system specially in case of hyperstimulation.

Drawbacks of vaginal insert includes more hyperstimulation, higher cost and cold storage failure, which decreases efficacy of the drug. Another unanticipated drawback was dropout rate of device. Vaginal insert did not prove to be better than intracervical gel on the whole when overall outcome of induction was considered. The present study was carried on relatively small number of patients, further studies with larger sample size are needed to establish these results.

Sustained release vaginal insert appears to be a more attractive option than gel therefore this study was initiated, however we did not find the overall results to be more rewarding.

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